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	ROCHE MOLECULAR SYSTEMS INC			SHAW, AMANDA MARIE	
PATENT LAW 1145 ATLANT	V DEPARTMENT TIC AVENUE		ART UNIT	PAPER NUMBER	
ALAMEDA, O	CA 94501		1634		
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Please find below and/or attached an Office communication concerning this application or proceeding.

	Application No.	Applicant(s)			
· .	10/635,171	HEINDL ET AL.			
Office Action Summary	Examiner	Art Unit			
	Amanda M. Shaw	1634			
The MAILING DATE of this communication app	ears on the cover sheet with the c	orrespondence address			
Period for Reply A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION. - Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication. - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication. - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any					
earned patent term adjustment. See 37 CFR 1.704(b). Status					
1) Responsive to communication(s) filed on 2a) This action is FINAL . 2b) ☐ This	_· action is non-final.	·			
20/C3 11110 dollars 10 1 1111 1211	3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is				
closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11, 453 O.G. 213.					
Disposition of Claims					
4) Claim(s) 1-27 is/are pending in the application.					
4a) Of the above claim(s) <u>16-26</u> is/are withdrawn from consideration.					
5) Claim(s) is/are allowed.					
6)⊠ Claim(s) <u>1-15 and 27</u> is/are rejected.					
7) Claim(s) is/are objected to.	,—				
8) Claim(s) are subject to restriction and/o	r election requirement.				
Application Papers					
9) The specification is objected to by the Examiner.					
10)⊠ The drawing(s) filed on <u>8/6/2003</u> is/are: a)⊡ accepted or b)⊠ objected to by the Examiner.					
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).					
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).					
11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.					
Priority under 35 U.S.C. § 119					
 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). a) All b) Some * c) None of: 1. Certified copies of the priority documents have been received. 2. Certified copies of the priority documents have been received in Application No. 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)). * See the attached detailed Office action for a list of the certified copies not received. 					
Attachment(s) 1) ☑ Notice of References Cited (PTO-892) 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 3) ☑ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 12/31/03 &12/10/04.	4) Interview Summary Paper No(s)/Mail D 5) Notice of Informal F 6) Other:				

Art Unit: 1634

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I in the reply filed on January 12, 2006 is acknowledged. Accordingly, Claims 1-15 and 27 have been examined herein.

Drawings

2. The drawings are objected to because the headings and the numbers on the x and y axis for Figures 1-7 are unclear. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required

Art Unit: 1634

corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

3. Claims 15 and 27 are objected to because of the following informalities: Claims 15 and 27 refer to the pair of hybridization probes of Claim 1, but Claim 1 is drawn to a composition comprising a pair of hybridization probes hybridizing to a target nucleic acid sequence. As stated in MPEP 608.01(n), "The test as to whether a claim is a proper dependent claim is that it shall include every limitation of the claim from which it depends (35 U.S.C. 112, fourth paragraph) or in other words that it shall not conceivably be infringed by anything which would not also infringe the basic claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a pair of FRET hybridization probes hybridizing to a target nucleic acid sequence, where each probe has a complementary nucleotide sequence entity, either a FRET donor entity or a FRET acceptor entity, and a spacer entity wherein the spacer on the first probe is capable of forming non covalent interactions (i.e. hydrogen bonding, hydrophilic interactions) with

Art Unit: 1634

the spacer entity of second probe when the two probes are adjacent to each other, does not reasonably provide enablement for the two spacer probes to react ionically with each other. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn broadly to a composition comprising a pair of FRET hybridization probes hybridizing to a target nucleic acid sequence, where each probe has a complementary nucleotide sequence entity, either a FRET donor entity or a FRET acceptor entity, and a spacer entity wherein the spacer entity on the first probe is capable of interacting with the spacer entity of second probe when the two probes are adjacent to each other. The claims are further limited by the recitation that the spacer entities interact with each other by non covalent interactions (i.e. H-bonding, hydrophobic interactions, and ionic interactions).

Nature of the Invention

Art Unit: 1634

The claims are drawn broadly to a composition comprising a pair of FRET hybridization probes hybridizing to a target nucleic acid sequence, where each probe has a complementary nucleotide sequence entity, either a FRET donor entity or a FRET acceptor entity, and a spacer entity wherein the spacer entity on the first probe is capable of forming non covalent interactions with the spacer entity of second probe when the two probes are adjacent to each other. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches a composition comprising a pair of FRET hybridization probes hybridizing to a target nucleic acid sequence, where each probe has a complementary nucleotide sequence entity, either a FRET donor entity or a FRET acceptor entity, and a spacer entity wherein the spacer entity on the first probe is capable of forming non covalent interactions with the spacer entity of second probe when the two probes are adjacent to each other. The specification (page 11) discloses that the non covalent interactions between the two spacers of a pair of FRET hybridization probes nucleotide base pairing interactions and preferably A/T base pairing interactions. The specification further teaches (page 13) that other spacer entities besides nucleotide residues that interact via non covalent interactions include those that involve all kinds of hydrogen bonding, for example polypeptide interactions, and all kinds of hydrophobic interactions, for example those based on-CF.sub.2 groups

Art Unit: 1634

and ionic attractions. Thus, spacers with non covalent interactions involve all kinds of hydrogen bonding (like in peptides/oligonucleotides) and all kinds hydrophobic interactions (like aryl-aryl, alkyl-alkyl interaction or attraction between fluorinated hydrocarbons). lonic interaction can be used if one of the spacer is negatively charged and the other spacer is positively charged.

Accordingly, the specification is enabled for a composition comprising a pair of FRET hybridization probes hybridizing to a target nucleic acid sequence, where each probe has a complementary nucleotide sequence entity, either a FRET donor entity or a FRET acceptor entity, and a spacer entity wherein the spacer entity on the first probe is capable of forming non covalent interactions with the spacer entity of second probe when the two probes are adjacent to each other.

The specification and prior art do not teach a pair of probes containing spacer entities that will interact with each other ionically if when one spacer is positively charged and the other spacer is negatively charged. Furthermore, the specification does provide a specific example where this phenomenon occurs.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

It is unpredictable as to whether a composition comprising a pair of FRET hybridization probes hybridizing to a target nucleic acid sequence, where each probe has a complementary nucleotide sequence entity, either a FRET donor entity or a FRET acceptor entity, and a spacer entity wherein the spacer entity on the first probe is capable of forming ionic interactions with the spacer entity of second probe when the two probes are adjacent to each other could actually interact ionically. It is well known

Art Unit: 1634

in the art that hybridization assays typically occur in reaction mixtures that have salt. The phrase "stringent hybridization conditions" is well known in the art and refers to conditions under which a probe will hybridize to its target subsequence, typically in a complex mixture of nucleic acid, but to no other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures. Generally, stringent conditions are selected to be about 5-10°C lower than the thermal melting (Tm) point for the specific sequence at a defined ionic strength pH. Stringent conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes and at least about 60°C for long probes (Fischer para 0046). The presence of ions in the solution make it unpredictable that the spacer could interact with each other because the ions would be interacting with the spacer entities.

The specification teaches that spacers with ionic interactions can be used if one of the spacer is negatively charged and the other spacer is positively charged (page 13). However there is no specific example of two spacers, where one is negatively charged and the other is positively charged, that are able to interact with. The specification simply states that these exist and does not provide sufficient guidance for identifying potential linkers that could interact this way.

Amount of Direction or Guidance Provided by the Specification:

Working Examples:

Art Unit: 1634

Again, the specification teaches a composition comprising a pair of FRET hybridization probes hybridizing to a target nucleic acid sequence, where each probe has a complementary nucleotide sequence entity, either a FRET donor entity or a FRET acceptor entity, and a spacer entity wherein the spacer entity on the first probe is capable of forming ionic interactions with the spacer entity of second probe when the two probes are adjacent to each other. There are no specific examples provided in the specification of spacers that form ionic interactions with each other. Further, there are no working examples provided in the specification in which spacers which form ionic interactions with each other are used.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation." In re Wright 990 F.2d 1557, 1561. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in Genetech Inc. v Novo Nordisk 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

Art Unit: 1634

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification does not teach specific types of spacers that can form ionic interactions with each other. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 10, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Nadeau et al (U.S. Patent 6130047).

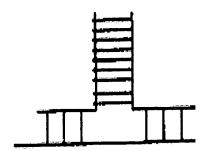
Regarding Claim 1, Nadeau et al teach a composition comprising a pair of FRET hybridization probes capable of hybridizing to a target nucleic acid sequence. Each probe comprises a nucleotide sequence entity that is complementary to a region of the target, a fluorescent entity (FRET donor or acceptor), and a spacer entity that connects the nucleotide sequence entity and the fluorescent entity; wherein the FRET hybridization probes hybridize adjacently to each other on the target nucleic acid; and wherein the spacer entities of the FRET hybridization probes are capable of forming non covalent interactions with each other. Specifically Nadeau et al teach a detector nucleic

Art Unit: 1634

acid comprising a 3-way oligonucleotide junction structure and two donor/acceptor dye pairs. The detector nucleic acid comprises: a target oligonucleotide (labeled at the 5' end with fluorescein), a first oligonucleotide (labeled at the 3' end with fluorescein), and a second oligonucleotide (labeled at the 5' and 3' ends with dabcyl) (Example 3 and Figure 3). The following illustrates the teachings of Nadeau: the nucleotides in red are the linkers. As you can see they hybridize to each other. The first oligo is attached to a flourescein and the second is attached to dabcyl. The blue part of the first oligonucleotide hybridizes the target sequence and the green part of the second oligonucleotide hybridizes adjacent to the first oligonucleotide on the target sequence. This would look like the figure below.

Target SEQ 5'flourescein-GGAGCGAAGTGTCCTGGCTAGAGTCTTCAAATATCAGAGCTTTACCTAACAA 3'
First Oligonucleotide 5'GCCAGGACACGGAGAGG-flourescein-3'

Second Oligonucleotide 5' dabcyl-CCTCTCCCGCTCC-dabcyl 3'



Regarding Claim 2, Nadeau et al teach composition wherein the non covalent interactions between the linkers are nucleotide base pairing interactions. Specifically

Art Unit: 1634

Nadeau et al teach that the linkers (i.e. oligonucleotides) are involved in base pairing (Example 3, and Figure 3).

Regarding Claim 3, Nadeau et al teach that the nucleotide base pairing interactions are A/T base pairing interactions. Specifically the oligos that Nadeau et al teach contain 2 A/T base pairs and 5 C/G base pairs (Example 3).

Regarding Claim 5, Nadeau et al teach a wherein FRET acceptor entity is a Dabcyl or a Black Hole Quencher. Specifically Nadeau et al teach that the FRET acceptor is a dabcyl (Example 3).

Regarding Claim 10, Nadeau et al teach a composition wherein one of the hybridization probes is labeled at the 3' terminal end and the other of the hybridization probes is labeled at the 5' terminal end, such that upon hybridization of the probes to the target nucleic acid and excitation of the FRET donor entity, fluorescent resonance energy transfer to the FRET acceptor entity can occur Specifically Nadeau et al teach that the first oligonucleotide was labeled at the 3' end with fluorescein, and a second oligonucleotide was labeled at the 5' and 3' ends with dabcyl (Example 3).

Regarding Claim 27, Nadeau et al teach a reaction mixture for use in a dependent nucleic acid amplification reaction, comprising, in a solution: a pair of hybridization probes and at least one other component selected from the group consisting of nucleic acid amplification primers, a template dependent nucleic acid polymerase, deoxynucleoside triphosphates and a buffer suitable for use in a template dependent nucleic acid amplification reaction. Specifically Nadeau et al teach they

Art Unit: 1634

prepared a solution containing, 50 mM TRIS-HCI, pH 8.0, 10 mM MgCl₂, 50 mM NaCl,

10 mM dTTP, 10 mM dCTP, 10 mM dGTP, 10 mM dATP, 5 units exo- Klenow, and

varying amounts of the 3-way junction detector nucleic acid were prepared and placed

in an SLM 8100 fluorometer with the sample chamber preheated to 37°C (Example 3).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nadeau et al (U.S. Patent 6130047) in view of Wittwer (U.S. Patent 6140054).

The teachings of Nadeau are presented above. However, Nadeau et al do not teach a set of FRET probes wherein the fluorescent entities of the probes are selected from the group consisting of fluorescein/Cy5, fluorescein/LC Red 640, fluorescein/LC Red 705, and fluorescein/JA286.

However, Wittwer et al teach that acceptable fluorophore pairs for use as fluorescent resonance energy transfer pairs are well know to those skilled in the art and include, but are not limited to, fluorescein/rhodamine, phycoerythrin/Cy7, fluorescein/Cy5, or fluorescein/Cy5.5.

Art Unit: 1634

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nadeau by using one of the flourophore pairs suggested by Wittwer because they are an equally effective means for detecting nucleotides via FRET technology.

Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over 7. Nadeau et al (U.S. Patent 6130047) in view of Fisher (U.S. Patent 6130047).

The teachings of Nadeau are presented above. However, Nadeau et al do not teach a composition wherein at least one of the hybridization probes includes a nucleotide having a non-natural base selected from the group consisting of a 7deazapurine, a diamino purine and a C-nucleotide.

However Fisher et al teach during primer and probe experiments higher affinity and/or specificity to complementary nucleic acids may be achieved by the using nucleobase analogs (i.e. isoguanine and 7-deaza-isoguanine) (Column 8, lines 4-22).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nadeau et al so as to have used a probe containing atleast one non naturally occurring base in order to have achieved the benefits set forth by Fisher which include improving the affinity and specificity of the probe hybridizing to the complementary nucleic acids.

Art Unit: 1634

8. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nadeau et al (U.S. Patent 6130047) in view of Acton et al (U.S. Patent 6228581).

The teachings of Nadeau are presented above. However, Nadeau et al do not teach wherein at least one of the hybridization probes includes a modified sugarphosphate backbone that contains either a 2-O methyl group or a phosphothioate.

However, Actor et al teach that nucleic acids which can be used as probes or primers can be modified to become more stable. Examples of such nucleic acids are phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (Column 24, lines 65-68).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nadeau et al so as to have used a probe containing a modified sugar phosphate backbone in order to have achieved the benefits set forth by Fisher which include having a more stable nucleic acid.

9. Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nadeau et al (U.S. Patent 6130047) in view of Ogawa et al (Journal of American Chemical Society).

The teachings of Nadeau are presented above. However, Nadeau et al do not teach a composition wherein the non covalent interactions are hydrophobic interactions (i.e.aryl/aryl, alkyl/alkyl or fluorinated hydrocarbons).

Art Unit: 1634

However, Ogawa et al teach unnatural hydrophobic base pairs (i.e. trimethylphenyl (TM) nucleoside or dimethylophenyl (DM) nucleoside). To optimize the stability and selectivity of the unnatural pair, a variety of TM and DM derivatives were also made. Modification included increased aromatic surface area, alkyl group substitution, and the inclusion of minor groove H bond acceptors (Page 3275).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nadeau et al so as to have used a spacer capable of forming hydrophobic interactions in order to have achieved the benefits set forth by Ogawa which include more stable and selective base pair interactions.

10. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nadeau et al (U.S. Patent 6130047) in view of Urdea et al (U.S. Patent 5635352).

The teachings of Nadeau are presented above. However, Nadeau et al do not teach a composition wherein said spacer entity is branched.

However, Urdea et al teach a composition wherein spacer entity is branched. Specifically Urdea et al teach amplification multimers, which are constructed so as to contain a first segment that hybridizes specifically to the nucleic acid, and a multiplicity of second segments that hybridize specifically to a labeled probe. The multimers may be either linear or branched. Branched multimers may be in the shape of a fork or a comb, with comb-type multimers preferred (Column 2, lines 1-14).

Art Unit: 1634

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nadeau et al so as to have used branched linkers in order to provide signal amplification in hybridization assays through networks of labeled probes. Branched mulitmers provide a convenient way to covalently attach more than one dye to an oligonucleotide.

11. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nadeau et al (U.S. Patent 6130047) in view of Ahern (The Scientist).

The teachings of Nadeau are presented above. However, Nadeau et al do not teach the packaging of FRET probes along with at least one other component selected from the group consisting of nucleic acid amplification primers, a template dependent nucleic acid polymerase, deoxynucleoside triphosphates and a buffer suitable for use in a template dependent nucleic acid amplification reaction into a kit.

However, reagent kits for performing nucleotide detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, Ahern discloses the general concept of kits for performing detection methods and teaches that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Ahern (page 22) also teaches that kits provide the benefits of cost-effectiveness and time efficiency. Accordingly, it would have been prima_facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the FRET probes along with at least one other component selected from the group consisting of nucleic acid amplification primers, a template dependent nucleic

Art Unit: 1634

acid polymerase, deoxynucleoside triphosphates or a buffer in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to detect nucleotide sequences using FRET probes.

Conclusion

12. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw Examiner Art Unit 1634 March 6, 2006